READ IT BEFORE YOUR PATIENTS

Head & neck

Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase III trial

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BACKGROUND

Chemoradiotherapy is the standard of care for unresected locally advanced squamous cell carcinoma of the head and neck. We aimed to assess if addition of avelumab (anti-PD-L1) to chemoradiotherapy could improve treatment outcomes for this patient population.

METHODS

In this randomised, double-blind, placebo-controlled, phase III study, patients were recruited from 196 hospitals and cancer treatment centres in 22 countries. Patients aged 18 years or older, with histologically confirmed, previously untreated, locally advanced squamous cell carcinoma of the oropharynx, hypopharynx, larynx, or oral cavity (unselected for PD-L1 status), an Eastern Cooperative Oncology Group performance status score of 0.0 or 1.0, and who could receive chemoradiotherapy were eligible. Patients were randomly assigned (1:1) centrally by means of stratified block randomisation with block size four (stratified by human papillomavirus status, tumour stage, and nodal stage, and done by an interactive response technology system) to receive 10 mg/kg avelumab intravenously every two weeks plus chemoradiotherapy (100 mg/m2 cisplatin every three weeks plus intensity-modulated radiotherapy with standard fractionation of 70 Gy [35 fractions during seven weeks]; avelumab group) or placebo plus chemoradiotherapy (placebo group). This was preceded by a single 10 mg/kg avelumab or placebo lead-in dose given seven days previously and followed by 10 mg/kg avelumab or placebo every two weeks maintenance therapy for up to 12 months. The primary endpoint was progression-free survival by investigator assessment per modified Response Evaluation Criteria in Solid Tumours, version 1.1, in all randomly assigned patients. Adverse events were assessed in patients who received at least one dose of avelumab or placebo. This trial is registered with ClinicalTrials.gov, NCT02952586. Enrolment is no longer ongoing, and the trial has been discontinued.

FINDINGS

Between 12 Dec 2016, and 29 Jan 2019, from 907 patients screened, 697 patients were randomly assigned to the avelumab group (n=350) or the placebo group (n=347). Median follow-up for progression-free survival was 14·6 months (IQR 8·5-19·6) in the avelumab group and 14·8 months (11·6-18·8) in the placebo group. Median progression-free survival was not reached (95% CI 16·9 months-not estimable) in the avelumab group and not reached (23·0 months-not estimable) in the placebo group (stratified hazard ratio 1·21 [95% CI 0·93-1·57] favouring the placebo group; one-sided p=0·92). The most common grade 3.0 or worse treatment-related adverse events were neutropenia (57 [16%] of 348 patients in the avelumab group vs 52 [15%] of 344 patients in the placebo group), mucosal inflammation (50 [14%] vs 45 [13%]), dysphagia (49 [14%] vs 47 [14%]), and anaemia (41 [12%] vs 44 [13%]). Serious

treatment-related adverse events occurred in 124 (36%) patients in the avelumab group and in 109 (32%) patients in the placebo group. Treatment-related deaths occurred in two (1%) patients in the avelumab group (due to general disorders and site conditions, and vascular rupture) and one (<1.0%) in the placebo group (due to acute respiratory failure).

INTERPRETATION

The primary objective of prolonging progression-free survival with avelumab plus chemoradiotherapy followed by avelumab maintenance in patients with locally advanced squamous cell carcinoma of the head and neck was not met. These findings may help inform the design of future trials investigating the combination of immune checkpoint inhibitors plus CRT.